Exposure and response analysis of aleglitazar on cardiovascular risk markers and safety outcomes: An analysis of the AleCardio trial

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Abstract
Aims: The AleCardio trial aimed to characterize the efficacy and safety of peroxisome proliferator-activated receptor-αγ agonist aleglitazar in patients with type 2 diabetes mellitus and acute coronary syndrome. The trial terminated early because of futility and safety signals. We evaluated whether the safety signals could be attributed to increased exposure to aleglitazar.

Materials and Methods: The AleCardio trial enrolled 7226 patients to receive aleglitazar 150 μg or matching placebo on top of standard care. A population pharmacokinetic analysis was conducted in a pharmacokinetic substudy to identify covariates that explained interindividual variability in exposure. Subsequently, the effect of these covariates on surrogate and clinical outcomes was assessed in the full patient population.

Results: Concomitant administration of clopidogrel was identified as a covariate that influenced the apparent clearance of aleglitazar. Patients using clopidogrel had a mean predicted area under the plasma-concentration-time curve (AUC0–24h) of 174.7 ng h/mL (SD: ±112.9 ng h/mL) versus 142.2 ng h/mL (SD: ±92.6 ng h/mL) in patients without clopidogrel. The effect of aleglitazar compared with placebo on HbA1c, haemoglobin, serum creatinine and adiponectin was modified by concomitant clopidogrel use (P for interaction 0.007, 0.002, <0.001 and < 0.001, respectively).
Conclusions: Concomitant use of clopidogrel was identified as a covariate that explained interindividual variability in exposure to aleglitazar. Patients using clopidogrel showed an additional lowering of HbA1c, at the expense of an additional decrease in haemoglobin, and an increase in serum creatinine and adiponectin. Clopidogrel is a moderate inhibitor of CYP2C8. Because aleglitazar is metabolized by CYP2C8, a pharmacokinetic interaction could explain differences in exposure and response to aleglitazar.

Keywords: aleglitazar, exposure response, peroxisome proliferator-activated receptor, PK-PD, randomized controlled trial

1 | INTRODUCTION

Peroxisome proliferator-activated receptor (PPAR)-α receptors regulate glucose homeostasis, insulin sensitivity and lipid storage while PPAR-γ receptors regulate fatty acid β-oxidation and energy homeostasis. Aleglitazar is a dual agonist of the PPAR-α and -γ receptors and has been shown to improve glycaemic variables and lipid profile in patients with type 2 diabetes mellitus.1,2 However, PPAR-γ activation may lead to sodium and fluid retention, particularly in patients with type 2 diabetes who are prone to sodium and fluid retention.3

The AleCardio trial was designed to determine whether aleglitazar compared with placebo reduces cardiovascular morbidity and mortality among patients with type 2 diabetes mellitus and a recent acute coronary syndrome (ACS).4 The trial was terminated early because of futility for efficacy and increased rates of congestive heart failure, bone fractures and gastrointestinal haemorrhage associated with aleglitazar.5 The increased rate of congestive heart failure is probably a result of sodium and fluid retention following PPAR-γ activation.

Patients assigned to aleglitazar received a fixed dose of 150 μg daily. It is unknown whether increased exposure to aleglitazar contributed to the safety findings in the trial. The aim of the current study was therefore to characterize the interindividual variation in exposure to aleglitazar, to determine the factors associated with aleglitazar exposure, and to assess the association between aleglitazar exposure and safety and efficacy measures.

2 | MATERIALS AND METHODS

2.1 | Study design and patient population

The design of the AleCardio trial (Clinicaltrials.gov trial registration number: NCT01042769; registration date: January 6, 2010) has been reported previously.3,5 The study protocol of the AleCardio trial was approved by the appropriate national and institutional regulatory and ethical boards.

Briefly, qualifying patients were hospitalized for ACS (defined as unstable angina or acute myocardial infarction) with established or newly diagnosed type 2 diabetes mellitus. Exclusion criteria included symptomatic heart failure or hospitalization with a primary diagnosis of heart failure within the previous year, severe peripheral edema, an estimated glomerular filtration rate (eGFR) of less than 45 mL/min/1.73 m², or treatment with another PPAR agonist. A total of 7226 patients at 720 sites in 26 countries were enrolled between February 2010 and May 2012. Between hospital discharge after ACS and 12 weeks thereafter, patients were randomized in a double-blind, 1:1 ratio to receive aleglitazar (150 μg per day) or matching placebo on top of standard therapy. Patients were asked to take study medication at the same time of the day throughout the study, but a specific time of day or relation to meals was not specified. The primary efficacy endpoint was time to cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke. Principal safety endpoints were hospitalization caused by heart failure and changes in renal function. Efficacy measures and hospitalization for heart failure were adjudicated by a blinded clinical events committee. Other adverse events of special interest were edema, bone fractures, hypoglycaemia and malignancies. Upon the recommendation of the data and safety monitoring board, the trial was terminated in July 2013 with a median follow-up of 2 years because of futility for efficacy and increased rates of safety endpoints with aleglitazar.

In a pharmacokinetic substudy, plasma samples were collected in 515 of 3616 patients treated with aleglitazar. In this substudy, patients were divided into two groups with different pharmacokinetic sampling schemes. In the first group (n = 117), a total of four samples were collected at predose and between 30–120, 121–180 and 181–240 minutes after administration of aleglitazar at a single study visit. In the second group (n = 398), again a total of four samples were collected; however, in this group a sample was collected predose and postdose at two consecutive study visits. For the purpose of analysis, data of both groups were pooled. Actual dosing times and sampling times were recorded. Pharmacodynamic samples were collected for all patients throughout the AleCardio trial at multiple study visits.

2.2 | Population pharmacokinetic analysis

A stepwise approach was used to develop the pharmacokinetic model. Different structural models with linear absorption and elimination
processes were explored, including one- and two-compartment models. Parameter estimates were obtained using first-order conditional estimation with interaction. Interindividual variability (IIV) was incorporated in the model, assuming a log-normal distribution of the random effects on the model parameters. Also, covariance between random effects was formally tested. Additive, proportional and combination residual variability models were tested. Covariate screening was performed for the following covariates: eGFR at baseline, body weight (at baseline and time-dependent), use of different types of co-medication at baseline, occasion of study visit, food effect (fasted vs. non-fasted state), age, sex, race, ethnicity and smoking status (both smoking at baseline and duration of smoking). Covariates were explored using correlation matrices of the empirical Bayes estimates of the parameters versus potential covariates. Significant covariates ($P < 0.05$) were taken forward in the model development. Continuous covariates were modelled as log-normal distributed, median-normalized covariates. For discrete covariates, separate population parameters were estimated. For body weight, allometric scaling with and without fixed power coefficients was explored. Model selection and evaluation was based on the minimum objective function value (MOFV), standard goodness-of-fit plots, residual standard error (RSE) of the population parameter estimates and the coefficient of variation (CV) of the interindividual random effects.

### 2.3 | Pharmacodynamic analysis

#### 2.3.1 | Surrogate outcomes

After the population pharmacokinetic analysis, we investigated the exposure-response relationship between aleglitazar and several surrogate outcomes. Not only the patients included in the pharmacokinetic substudy, but all patients included in the AleCardio trial were evaluated. HbA1c, the primary efficacy risk marker, haemoglobin and body weight, proxies for sodium retention, and serum creatinine, adiponectin and triglycerides, were included in the exposure-response analysis. At first, for each of these surrogate outcomes, change of baseline over time was explored graphically. Second, patients were stratified based on covariates, identified in the population pharmacokinetic analysis, which were able to explain variability in exposure to aleglitazar. Continuous and discrete covariates required a different approach. For discrete covariates, patients were stratified per treatment arm, placebo or aleglitazar, and per covariate. For continuous covariates, patients were stratified per treatment arm and per quartile of the covariate. Third, a one-way analysis of covariance (ANCOVA) model was used to compare the effect of aleglitazar versus placebo per group. To determine if the aleglitazar treatment effect was modified by the covariate of interest, an interaction term between treatment group and the covariate of interest was added to the ANCOVA model. It was assumed that the effect of aleglitazar on cardiovascular risk markers was maximal after 6 months of treatment. Therefore, in the ANCOVA analysis, initial change from baseline until month 6 was used. Treatment arm and covariate stratum were included as fixed effects.

#### 2.3.2 | Clinical outcomes

The effects of covariates that influenced exposure were further explored on hard outcomes that caused the early termination of the AleCardio trial. The safety measures—hospitalization for heart failure, gastrointestinal haemorrhage and bone fractures—were evaluated using Cox proportional hazard models. All patients were stratified based on the approach described under surrogate outcomes. Treatment, covariate stratum and the interaction between treatment and covariate stratum were included in the models. Hazard ratios including 95% confidence intervals were estimated for all patients and for the stratified patient populations.

All data preparation and presentation was performed using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria). The population pharmacokinetic analysis was conducted using NONMEM version 7.3.0 (ICON Development Solutions, Ellicott City, MD, USA). The ANCOVA and Cox-proportional hazard models were performed in R, using the car package version 2.1.6 and survival package version 2.41–3, respectively.

### 3 | RESULTS

#### 3.1 | Population pharmacokinetic analysis

In total, 1855 plasma samples collected from 514 patients in the aleglitazar group were used for the pharmacokinetic analysis. Of these, 94 samples were excluded based on concentration below the lower limit of quantification ($n = 59$), insufficient volume to assay the sample ($n = 13$), missing dosing information ($n = 23$) and erroneous randomization to placebo instead of aleglitazar ($n = 1$). This resulted in the inclusion of 1761 samples from 514 patients, with one to four samples per patient. Most plasma samples were drawn 0–4 hours postdose ($n = 1005$) and most of the predose samples ($n = 693$) were drawn at least 20 hours after the preceding dose. The demographics of the patients included in the population pharmacokinetic analysis are presented in Table 1.

An exploratory analysis was conducted to summarize and visualize the measured concentrations of aleglitazar. The observed concentrations of aleglitazar were variable and covered a concentration range of 0.1 to 60.1 ng/mL at steady state (Figure 1). A two-compartment model best described the data of the pharmacokinetic substudy. IIV could be identified on both apparent clearance (CL/F) and apparent volume of distribution (V2/F) and a proportional residual error model proved to be best fit for purpose. A food effect on the absorption rate constant (KA) and concomitant administration of clopidogrel on CL/F improved model fit significantly ($P < 0.05$). Allometric scaling with fixed power coefficients improved goodness-of-fit plots and was therefore included in the model.

In general, the individual trend of the data is well captured by the population pharmacokinetic model. Goodness-of-fit plots are provided in Figure S1 and parameter estimates are tabulated in Table 2. The goodness-of-fit plots indicated that the high concentrations appear to be slightly underestimated. However, population parameter
TABLE 1  Baseline characteristics of patients included in the AleCardio trial

<table>
<thead>
<tr>
<th></th>
<th>Pharmacokinetic analysis</th>
<th>Pharmacodynamic analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>With clopidogrel</td>
<td>Without clopidogrel</td>
</tr>
<tr>
<td></td>
<td>With clopidogrel</td>
<td>Without clopidogrel</td>
</tr>
<tr>
<td>Number of patients</td>
<td>420</td>
<td>94</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.3 (9.5)</td>
<td>59.5 (10.5)</td>
</tr>
<tr>
<td>Sex (males)</td>
<td>324 (77.1)</td>
<td>62 (66.0)</td>
</tr>
<tr>
<td>Smoker</td>
<td>90 (21.4)</td>
<td>14 (14.9)</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>7 (1.7)</td>
<td>8 (8.5)</td>
</tr>
<tr>
<td>Asian</td>
<td>99 (23.6)</td>
<td>21 (22.3)</td>
</tr>
<tr>
<td>Caucasian</td>
<td>302 (71.9)</td>
<td>64 (68.1)</td>
</tr>
<tr>
<td>Other</td>
<td>12 (2.9)</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>83.0 (19.2)</td>
<td>86.9 (22.9)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>7.9 (1.8)</td>
<td>8.0 (1.5)</td>
</tr>
<tr>
<td>Estimated glomerular</td>
<td>78.8 (20.1)</td>
<td>81.2 (22.5)</td>
</tr>
<tr>
<td>filtration rate (mL/min/1.73 m²)</td>
<td>79.3 (20.5)</td>
<td>81.2 (22.5)</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>139.2 (14.7)</td>
<td>136.0 (14.1)</td>
</tr>
<tr>
<td>LDL cholesterol (mmol/L)</td>
<td>2.0 (0.8)</td>
<td>2.1 (0.9)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>127.5 (17.2)</td>
<td>127.4 (17.0)</td>
</tr>
<tr>
<td>(mmHg)</td>
<td></td>
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</table>

The baseline characteristics are displayed for patients included in the population pharmacokinetic analysis and in the pharmacodynamic analysis. All variables are displayed as mean (SD), only sex, smoking status and race are displayed as number of patients (% of patients).

FIGURE 1  Aleglitazar exposure over time stratified by clopidogrel use (n = 514). Data are displayed as: Observations (○), mean population prediction (—) with 95% prediction interval

estimates were estimated with high precision as indicated by their low RSE, ranging from 4.2%–19.0%. The CV of CL/F was 57.1% with low shrinkage (6%). The CV for the IIIV on V2/F was high (587%) with accompanying high shrinkage (37%). As inclusion of IIIV on the V2/F improved the individual fit of the data in terms of MOFV, residuals and goodness-of-fit plots, it was decided to include this random effect
3.2.2 | Clinical outcomes

The influence of concomitant administration of clopidogrel with aleglitazar on clinical outcomes is displayed in Figure 3. The effect of aleglitazar compared with placebo on the risks of hospitalization for heart failure was modified by clopidogrel use (HR: 1.21, 95% CI: 1.04–1.40) in patients with concomitant clopidogrel use. Conversely, aleglitazar showed a trend for a decreased risk of hospitalization for heart failure (HR: 0.78, 95% CI: 0.57–1.06) among patients without using clopidogrel. No effect modification by clopidogrel was observed for bone fractures or gastrointestinal haemorrhage (Figure 3).

4 | DISCUSSION

A large variation between individuals was observed in the plasma concentrations of aleglitazar in the AleCardio trial. We found that the plasma concentration-time profile of aleglitazar was best described using a two-compartment model with first-order absorption, first-order elimination and allometric scaling. Using this model, we showed that part of the observed IIV could be attributed to a reduced
FIGURE 2  Absolute change in cardiovascular risk markers over time in aleglitazar and placebo randomized patients stratified by baseline clopidogrel use. A, HbA1c (%), B, serum creatinine (mg/dL), C, haemoglobin (g/L), D, body weight (kg), E, adiponectin (pmol/L), F, triglycerides (mmol/L). Data are displayed as mean absolute change per study visit with 95% confidence intervals.
clearance of aleglitazar in patients using clopidogrel concomitantly. The pharmacodynamic analysis revealed that patients receiving concomitant clopidogrel showed larger reductions in HbA1c and haemoglobin and a larger increase in serum creatinine and adiponectin compared with patients who did not use clopidogrel.

In this study we found that the observed variability between individuals in the plasma concentration-time profile of aleglitazar in the AleCardio trial population, after administration of the therapeutic 150 μg/day aleglitazar dose, covered the complete dose range of 20–900 μg/day observed in a prior study of patients with type 2 diabetes mellitus. The population pharmacokinetic model identified a food effect on the absorption rate constant that could partly explain the fast absorption. Under fasting conditions, the absorption rate constant increased by 23.9%. The absorption phase of aleglitazar was estimated with high precision (RSEs were 15.5% for KA and 6% for the food effect). Nevertheless, to our knowledge, dedicated clinical studies on the food effects of aleglitazar have not been published and therefore our results, obtained from a post hoc analysis, should be carefully interpreted. Nevertheless, they are in line with a mass-balance study that reported fast absorption under fasting conditions (tmax ranging from 0.47 to 1.0 hours). Alternatively, the fast absorption may be caused by a formulation effect because the mass-balance study used an oral aleglitazar solution.

Co-medication that could potentially influence the pharmacokinetics of aleglitazar was investigated as a covariate in the population pharmacokinetic model. Patients using both aleglitazar and clopidogrel showed a 16.4% lower apparent clearance, which results in a higher exposure to aleglitazar compared with patients solely treated with aleglitazar (AUC0–24 of 174.7, SD 112.9 ng h/mL and 142.2, SD 92.6 ng h/mL, respectively). Clopidogrel is an antiplatelet drug and is commonly prescribed in the treatment of ACS, which explains the large number of patients receiving clopidogrel in the AleCardio trial. The effect of clopidogrel on the apparent clearance of

<table>
<thead>
<tr>
<th>Surrogate Outcome</th>
<th>With clopidogrel</th>
<th>Without clopidogrel</th>
<th>Difference</th>
<th>P interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA1c (%)</td>
<td>−0.72 (−0.64 to −0.80)</td>
<td>−0.39 (−0.15 to −0.63)</td>
<td>−0.33 (−0.09 to −0.57)</td>
<td>0.007</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.14 (0.13 to 0.15)</td>
<td>0.07 (0.04 to 0.10)</td>
<td>0.06 (0.03 to 0.09)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Haemoglobin (g/L)</td>
<td>−7.11 (−6.46 to −7.76)</td>
<td>−3.78 (−1.74 to −5.82)</td>
<td>−3.33 (−1.19 to −5.47)</td>
<td>0.002</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>2.50 (2.28 to 2.72)</td>
<td>2.80 (2.09 to 3.51)</td>
<td>−0.3 (0.44 to −1.04)</td>
<td>0.434</td>
</tr>
<tr>
<td>Adiponectin (pmol/L)</td>
<td>10 286.7 (9912.7 to 10 660.7)</td>
<td>6910.4 (5717.6 to 8103.2)</td>
<td>3376.31 (2126.2 to 4626.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>−0.66 (−0.61 to −0.73)</td>
<td>−0.57 (−0.38 to −0.76)</td>
<td>−0.10 (0.09 to −0.30)</td>
<td>0.318</td>
</tr>
</tbody>
</table>

Data are displayed as placebo-corrected absolute change from baseline with aleglitazar to month 6 (mean difference with 95% CI).
aleglitazar may be explained by the metabolism of aleglitazar, which is converted by CYP2C8 and CYP2C19 into metabolites M1 and M6.\textsuperscript{12} Clopidogrel is an inhibitor of CYP2C8 and thus may reduce the clearance of aleglitazar.\textsuperscript{13} As plasma clopidogrel concentrations were not available, no individual exposure of clopidogrel could be incorporated in the model.

Only concomitant use of clopidogrel affected the exposure of aleglitazar. High aleglitazar exposure caused by concomitant administration of clopidogrel resulted in an additional beneficial effect on HbA1c, an additional decrease in haemoglobin and an additional increase in serum creatinine and adiponectin. The administration of clopidogrel alone does not affect these surrogates as no differences in these variables were observed in the placebo group between patients treated with or without clopidogrel. The reduction in haemoglobin probably reflects haemodilution from sodium and the fluid-retaining effects of aleglitazar, while the increase in serum creatinine has been shown to be completely reversible after cessation of aleglitazar and reflects a renal haemodynamic effect.\textsuperscript{5}

Our analysis also showed that patients with high aleglitazar exposure caused by concomitant administration of clopidogrel showed an increased risk of hospitalization for heart failure, whereas patients without concomitant clopidogrel showed a trend towards a risk reduction. This finding supports the idea that a pharmacokinetic interaction between aleglitazar and clopidogrel has contributed to the increased exposure, resulting in a larger degree of sodium retention and increased risk of edema and heart failure. Nonetheless, concomitant use of clopidogrel did not explain the increased rates of gastrointestinal events and bone fractures.

Overall, body weight increased with aleglitazar compared with placebo by a mean of approximately 4 kg at 24 months. Although there may have been some contribution to increased body weight from fluid retention, the major mechanism of weight gain with PPAR-\(\gamma\) agonists is an increase in adipose tissue mass.\textsuperscript{14} We found no significant interaction of clopidogrel and aleglitazar treatment on body weight. This neutral finding is unexplained, but might indicate that the aleglitazar concentration-adipose tissue remodelling relationship was insensitive to the changes in aleglitazar exposure induced by clopidogrel co-treatment.

The phase II dose-finding trials aimed to determine the optimal dose of aleglitazar and were conducted in patients with type 2 diabetes mellitus without ACS. These studies concluded that the optimal benefit/risk balance is achieved at a daily dose of 150 \(\mu\)g. The AleCardio trial included patients with type 2 diabetes mellitus and ACS. A majority of patients used clopidogrel in the AleCardio trial because of a recent ACS, which contributed to a different aleglitazar pharmacokinetic and pharmacodynamic profile in the phase III clinical trial population. It is at this point unclear if a lower dose of aleglitazar in the AleCardio trial could have resulted in a more favourable benefit/risk balance as we were not able to estimate aleglitazar exposure in all patients enrolled in the trial. Regardless, the lesson to be taken from this study is that dose finding should ideally be performed in the same population as the phase III clinical trial population.

The results of this study may have clinical implications for future and existing PPAR therapies. For example, it has been shown that the area under the plasma concentration-time curve of pioglitazone, a PPAR-\(\gamma\) agonist, increased 2.1-fold after administration of clopidogrel.\textsuperscript{15} This suggests that a clinically relevant interaction may be present between clopidogrel and pioglitazone. Further studies in high cardiovascular risk patients using pioglitazone and clopidogrel, such as those participating in the PROactive and IRIS cardiovascular outcome trials, may indicate whether this interaction modifies the effect of pioglitazone on biomarkers and clinical events.\textsuperscript{16,17}

Although the population pharmacokinetic model allowed for accurate description of the pharmacokinetic variables of patients included in the pharmacokinetic substudy, the model showed some bias in the structural model and a large unexplained IIV, mainly in the apparent volume of distribution. This translated into an underprediction of the plasma concentration of aleglitazar in the higher concentration range. As such, the presented model was less useful for simulating the pharmacokinetic profiles of the remaining 3101 patients exposed to aleglitazar, for whom no pharmacokinetic data were available. Consequently, a stratification strategy was applied for the pharmacodynamic analysis on all patients, based on the main determinants for differences in exposure to aleglitazar. As a large IIV remained unexplained in the population pharmacokinetic analysis, it cannot be excluded that we missed important covariates which also significantly contribute to the variability in exposure and response to aleglitazar. It is, therefore, not possible to make definitive conclusions about if aleglitazar exposure was related to other safety outcomes, including gastrointestinal haemorrhages and bone fractures. To simulate pharmacokinetic data of all individuals in phase III clinical trials, more informative pharmacokinetic sampling schemes should be developed. Ideally, three samples per slope of the absorption and elimination phases of the plasma concentration-time profile should be obtained throughout a phase III trial.

In conclusion, the population pharmacokinetic analysis of the AleCardio trial identified concomitant administration of clopidogrel and food effect as covariates that influence the pharmacokinetics of aleglitazar. Concomitant administration of clopidogrel resulted in an increased exposure of aleglitazar, an additional decrease in HbA1c—at the expense, however, of an additional decrease in haemoglobin—and an increase in serum creatinine and adiponectin. Clopidogrel is a moderate inhibitor of the CYP2C8 enzyme, and as aleglitazar is partially metabolized by the CYP2C8 enzyme, a pharmacokinetic interaction could explain the observed differences between patients with and without clopidogrel.

**ACKNOWLEDGMENTS**

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CONFLICT OF INTEREST

JVK, ICS and JS have no competing interests. HULH is a consultant to Abbvie, AstraZeneca, Boehringer Ingelheim, Fresenius, Gilead, Janssen, Merck, Mundipharma and Mitsubishi Tanabe. He received research support from AstraZeneca, Abbvie, Boehringer Ingelheim and Janssen. GGS, through his institution, has received research support from Resverlogix, Roche, Sanofi, and The Medicines Company. AML and DEG received research grants from F. Hoffmann-La Roche. SJN received research grants from Anthera, Amgen, AstraZeneca, Cer- enis, Eli Lilly, F. Hoffmann-La Roche, InfraReDx, LipoScience, Novartis, Resverlogix and Sanofi-Regeneron; consultant/advisory board: Abbott, Amgen, AstraZeneca, Atheronova, Boehringer Ingelheim, CSL Behring, Esperion, LipoScience, Merck, Novartis, Omthera, Pfizer Roche, Sanofi-Aventis and Takeda. AW and AS: employment: F. Hoffmann-La Roche. HW: honoraria: AstraZeneca, Roche and Pfizer.

AUTHOR CONTRIBUTIONS

J.V.K., H.J.L.H. and J.S. analyzed and interpreted the data and wrote the first draft of the manuscript. I.C.S., G.G.S., A.M.L., S.J.N., A.S., H.W., A.W. and D.E.G. designed the clinical trial, collected the data and contributed to critical revision of the manuscript.

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REFERENCES


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